A Comprehensive Review on Diabetes Mellitus

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Abstract- *About 400 million people across the world are diagnosed with diabetes mellitus and it is becoming a leading cause of death. As for India, the incidence rate is quite high standing at approximately 9.3%, which in effect means 74 million diabetes patients. This paper presents a general outline of diabetes, taking into account its epidemiology, pathophysiology as well as treatment options. It describes swiftly two main types of diabetes – a form of dependence on insulin which is known as Type 1, and a form predominantly associated with elevated insulin in the body while there are world guidelines, and lifestyle affection. This disease raises more issues within the health sectors regarding the treatment, for the treatment is affected in many ways where the current treatment does not cure the disease induced by insulin diabetes requires insulin chemical disorder does not heal by giving up medication other than insulin since oral counter agents most blood sugar levels and may also affect other parts of the body aside those parts depending on by diabetes the use of medications such as the insulin for the Type 1 management and oral agents for the Type 2 addressing the glucose toxicity goes mostly unmet as such treatment may be even injurious. The rising rate raise concerns about diabetes due to increase of urbanization westernization Of Food And immobility To make the general public aware of these changes and reduce their effects, Health education among clinicians. Finally, there tends to be a promotion to more all rounded solutions towards the management of diabetes which are also useful in treating such conditions as hypertension and renal failure since they have increased in population in the past few years.*

Keywords- Diabetes mellitus types, antidiabetic drug, epidemiology, pathophysiology, treatment, insulin diagnosis

I. INTRODUCTION

Diabetes mellitus is a serious public health concern that affects over 400 million people globally. Chronic microvascular, macrovascular, and neuropathic consequences that might be fatal are gradually brought on by this metabolic syndrome. Elevated blood glucose levels are caused by either a lack of insulin secretion, injury to the pancreatic β cell, or insulin resistance from not using insulin. (1,3).Numerous biological processes are impacted by diabetes, thus it is necessary to employ a variety of medication classes with distinct modes of action in order to maximize treatment for diabetic patients (2). Type 1 diabetes and type 2 diabetes are the two forms of diabetes mellitus. Type 1 diabetes is brought on by the immune system attacking the beta cells in the pancreas, whereas Type 2 diabetes is brought on by obesity, insulin resistance, and reduced insulin secretion.

Insulin-dependent diabetes mellitus (IDDM), also known as type 1 DM, is a condition in which the body is unable to produce insulin and the patient must currently use an insulin pump or inject insulin. "Juvenile diabetes" is another name for this. Insulin resistance, a disorder in which cells do not use insulin as intended, with or without a complete lack of insulin, is the cause of type 2 diabetes, also known as non-insulin-dependent diabetes mellitus (NIDDM). The term "adult-onset diabetes" was once used to describe this kind. Gestational diabetes, the third major form, which occurs on by elevated blood glucose levels in pregnant women who have never had diabetes before.It might appear before type 2 DM develops. Insulin and oral hypoglycemic medications are among the pharmacotherapy options currently available for the treatment of diabetes mellitus. By increasing glucose uptake and decreasing gluconeogenesis, these medications either increase the pancreatic secretion of insulin or lower plasma glucose concentrations. However these current drugs do not restore normal glucose homeostasis for longer period and they are not free from side effects such as hypoglycemia, kidney diseases, GIT problems, hepatotoxicity, heart risk problems, insulinoma and they have to take rest of life.(13)

Rapid cultural and social changes, population aging, urbanization, dietary changes, decreased physical activity, and other unhealthy lifestyle and behavioral patterns have all contributed to this issue, according to WHO (1994). Nearly every population in the world now has diabetes mellitus and impaired glucose tolerance, and this trend is growing worldwide (WHO, 1994).(16)

Types of diabetes mellitus

- **TYPE 1** Insulin dependent
- **TYPE 2** Non Insulin dependent

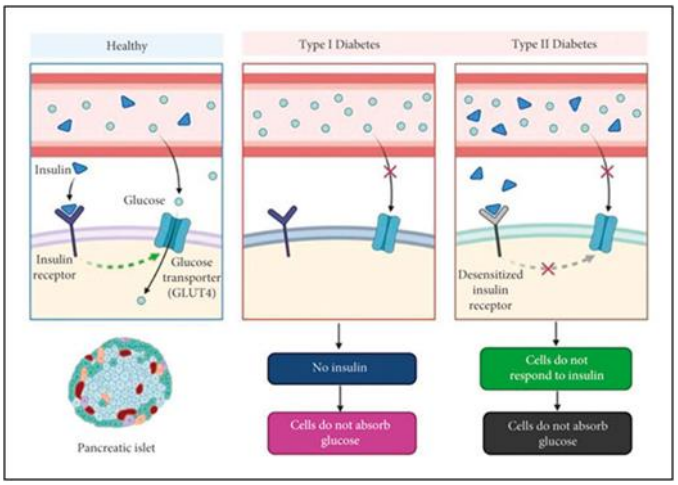


Fig. no 1: Difference of Healthy tissue and Type 1 & Type 2 Condition

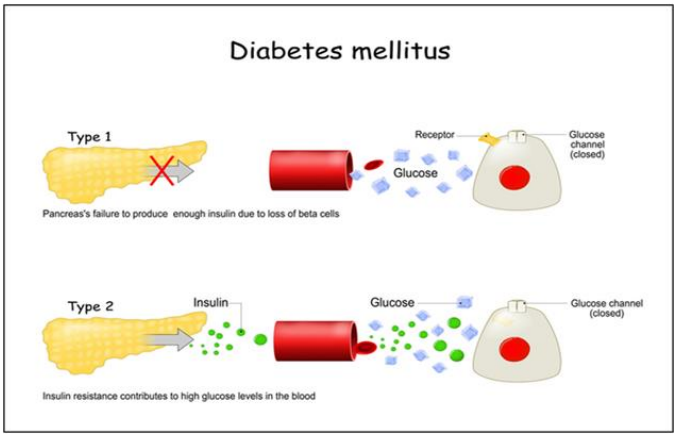


Fig no. 2 : Mechanisam of Type 1 and Type 2 Diabetes mellitus

Type 1: Diabetes mellitus (T1DM):

IDDM, It can occurs at any age commonly occurs in children patient require periodic doses of insulin Characterized by the autoimmune destruction of the pancreatic beta cells.

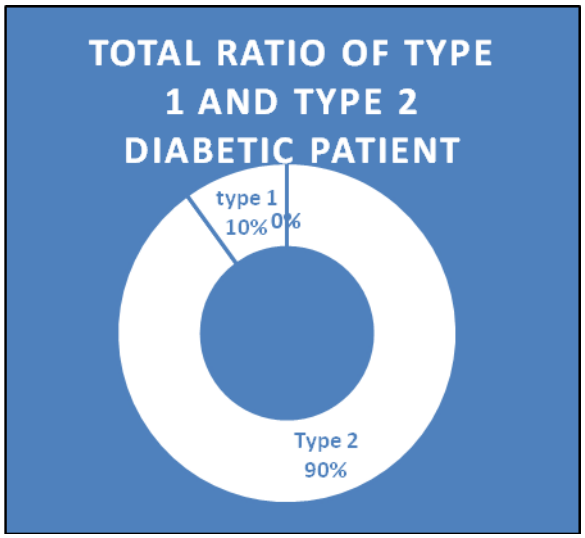
Before starting insulin therapy, the majority of patients had detectable anti-insulin antibodies, and about 85% of patients had circulating islet cell antibodies. The majority of islet cell antibodies target the pancreatic B cells' glutamic acid decarboxylase (GAD). The autoimmune destruction of pancreatic β-cells causes a lack of insulin secretion, which in turn causes the metabolic abnormalities linked to type 1 diabetes. Along with the loss of insulin secretion, T1DM patients also have abnormal pancreatic α-cell function and excessive glucagon secretion.

Type 2:

Diabetes mellitus(T2DM):Type 2 diabetes is non-insulin dependent diabetes mellitus (NIDDM). Impaired insulin secreation due to pancreatic beta cell dysfunction. There by increasing blood glucose level.(4)

Insulin Resistance with Relative Insulin Deficiency and Insulin Resistance with a Predominantly Insulin Secretory Defect are two types of type 2 diabetes. Ninety to 95 percent diabetes cases are of this type. It was previously known as adult-onset diabetes, type 2 diabetes, or non-insulin dependent diabetes. It includes people who have both relative (as opposed to absolute) insulin deficiency and insulin resistance. We do not yet know the specific etiologies. In this instance, b-cells are not destroyed by the immune system. The majority of patients are obese, and obesity in and of itself contributes to some level of insulin resistance.

With this diabetes, ketoacidosis frequently develops on its own. Because type 2 diabetes develops gradually and the patient does not exhibit any of the typical symptoms of the disease in its early stages, it is often left undetected. Here, there is a higher chance of developing macrovascular and microvascular complications. On the other hand, insulin levels in diabetic patients may be normal or higher. Consequently, these patients have impaired insulin secretion, which is insufficient to make up for insulin resistance. Insulin resistance may be improved by losing weight and/or treating hyperglycemia with medication. Age, obesity, and a lack of physical activity all increase the risk of developing this type of diabetes, which is not entirely understood.(16)



Pie chart 1 : Total ratio of Type 1 and Type 2 Diabetics patient of total diabetes patient

- **Causes:**

a. Genetic deficiency of beta cell function

b. Genetic deficiency in insulin action
c. Exocrine pancreas disease.(2)

An insulin therapy, oral hypoglycemic medications (eg.sulfony urea,biguanides,etc.), and lifestyle changes are the Traditional treatment method which have been played a fundamental role in managing diabetes.Although or even though their historical importance, these methods still have intrinsic control .The complex relationship between diabetes and comorbidities, as well as adverse reactions that patients re aware of, can make it difficult to achieve and maintain optimal glucose control. As a result, the envolving field of diabetes treatment necessitates a thorough reevalution that goes beyond the conventional framework. The limitation of conventional diabetes management techniques extend beyond blood sugar regulations. A more all-encompassing therapeutic approach was necessary for diabetes, which was recognized as a systemic alignment with significant consequences. Conventional treatment methods do not effectively target cardiovascular disease, which is a major contributor to the illness and death rates associated with diabetes. The difficulty is exacerbated by kidney-related problems, underscoring the need for treatments that address more than just blood glucose levels. (5).

- **Risk factor :**

Chart no. 1: Risk Factor

Sign & symptopms

Chart no. 2: Sign & symptoms

2.Epidemiology:

Numerous aspects of diabetes mellitus, including its natural history, prevalence, incidence, morbidity, and mortality in diverse populations worldwide, have been beneficially revealed by the study of epidemiology. By determining the disease's cause and potential preventive measures that could be put in place to stop or postpone its onset, it spread to epidemic proportions in both developed and developing countries. Regretfully, comparable improvements have not been achieved in the outcomes of public health initiatives for individual diabetic patients.

The study of epidemiology of Diabetes mellitus has been provide beneficial information on several aspects of this disease such as its natural history, prevalence, incidence, morbidity and mortality in various populations around the world. By determining the disease's cause and potential preventive measures that could be put in place to stop or postpone its onset, it spread to epidemic proportions in both developed and developing countries. Regretfully, comparable improvements have not been made to the public health outcomes for individual diabetic patients.(6)

According to 2019 figures from the International Diabetes Federation, 537 million persons worldwide are estimated to have diabetes. In 2020, diabetes was the ninth most common cause of death worldwide, accounting for roughly 2 million fatalities each year from both diabetes-related kidney disease and diabetes itself. According to WHO estimates, diabetes was the eighth greatest cause of mortality in 2012, accounting for 1.5 million deaths. However, high blood glucose and the increased risk of related complications (such as heart disease, stroke, and kidney failure) were responsible for an additional 2.2 million deaths globally. These complications frequently lead to premature death and

are frequently listed as the underlying cause on death certificates instead of diabetes.

India has the second highest number of people with diabetes. Diabetes currently affects more than 74 million Indians, which is more than 8.3% of the adult population. It is estimated to be around 57% of the current cases of diabetes to be undiagnosed. Among young and middle aged adults the prevalence of diabetes is 6.7% and prediabetes is 5.6% according to the National Family Health Survey-4. Nearly 1 million Indians die due to diabetes every year.

3.Pathophysiology:

Numerous hormones in the body keep glucose in its proper range. When the concentration of glucose rises, the pancreatic beta cell still secretes insulin. Insulin lower blood glucose level

a)by either increasing the uptake of glucose by the liver, muscle, and fat tissue, or
b)by preventing the liver from production glucose through glycogeniolysis and gluconeogenesis.(1)

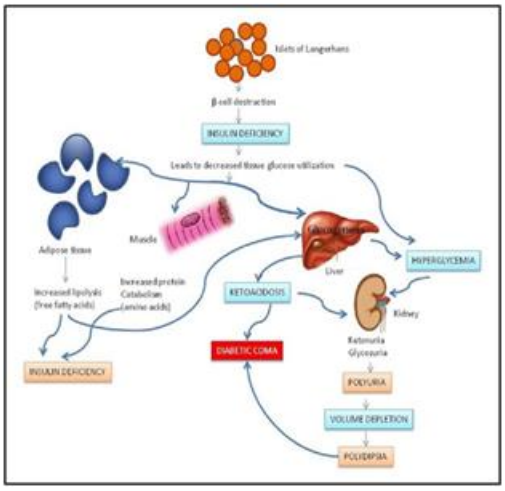


Fig 3: Pathophysiology of type 2 diabetes

Auto-immune destruction of the pancreatic cells that produce insulin by CD4+ and CD8+ T cell and macrophages infiltrating the islets is a hallmark of type 1 and type 2 diabetes. The presence of immune-competent and accessory cells in infiltrated pancreatic islet, the correlation between susceptibility to decision and the class II (immune response) genes of the major histocompatibility complex, and the presence of autoantibodies specific to islet are some of the characteristics that define type 1 diabetes mellitus as an auto-immune disease.(6)

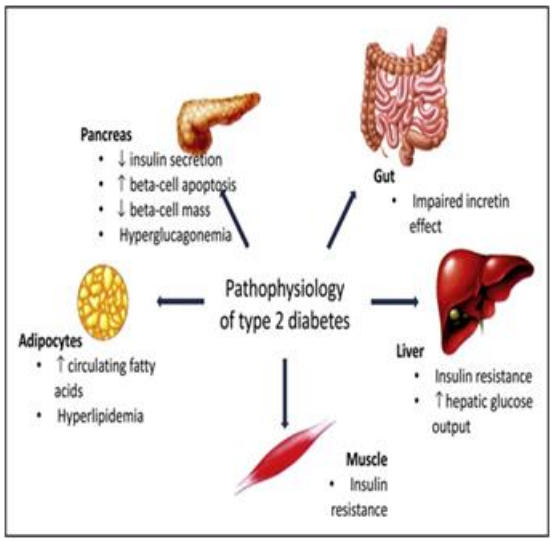
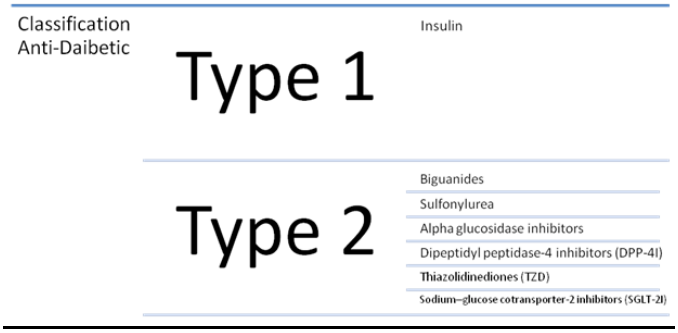


Fig 4: pathophysiology of type 1 diabetes

Classification :

Flow chart 3: Classification of Antidiabetic Drug use for both Type1 and Type 2



4.Treatment:

Type 1 DM : Insulin dependent .

Insulin and Its Types**.** There are various types of insulin available. The four main types are:

A) Short-acting insulin,
B)Intermediate-acting insulin,
C)Long-acting insulin,
D)Rapid-acting insulin.(3)

Insulin:

The pancreatic beta cell is the endogenous source of the hormone insulin. Patient with diabetes mellitus and type 1 diabetes have a complete lack of insulin, and patient with type 1 diabetes may also have less endogenous insulin produced. All patient with type 1 diabetes are dependent on insulin therapy for the rest of lives. Insulin is frequently used as

monotherapy as the disease worsens or as an adjuvant therapy to oral diabetic agents in patients with type 2 diabetes. Multiple types of insulin resulted from various modifications and substitutions made to the insulin molecule. This described an administered substance according to its pharmacodynamics and pharmacokinetics properties, including its duration, peak, and onset of action. Most importantly, they are divided into four categories: short acting, long acting, intermediate acting, and rapid acting. (9).

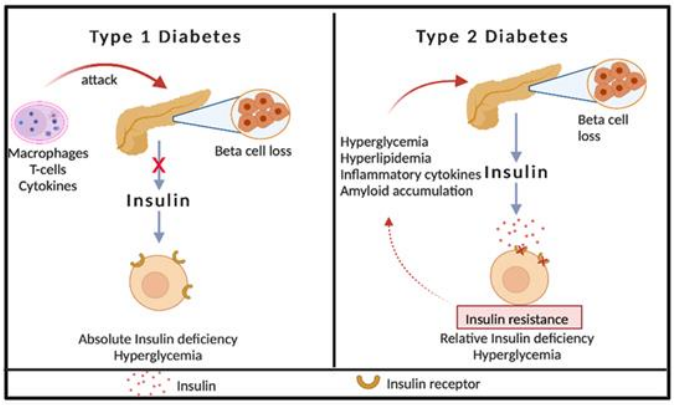


Fig. no 5: Role of Insulin in Type 1 and Type

Mechanism of action:

The common mechanism of action of Insulin is, it Binds to the insulin receptor which is having tyrosine kinase activity.

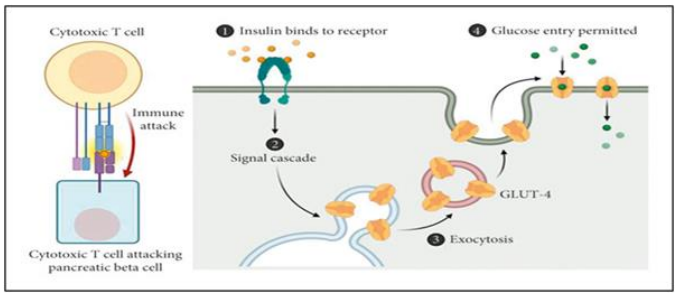
a) Insulin in hepatocytesincreasesconversion of glucose to glycogen.
b) In smooth or skeletal Muscle : it increases not only glycogen but also protein synthesis.
c) In Fatty tissues: increase Triglycerides synthesis and accumulation.
d) In general, the cell increases potassium uptake.(3)

- **Insulin Action:**

1. Onset: Time it takes for insulin to start working
2. Peak: Time of maximum insulin effect
3. Duration: Length of time insulin remains active

- **Administration:**

1. Subcutaneous injection (under the skin), although it can also be delivered intravenously in hospital settings (e.g., in an emergency or for tight glucose control).
2. Insulin pump
3. Inhalation (Afrezza)



- **Adverse Effects:**

1.*Hypoglycemia:* The most serious adverse effect of insulin therapy and the primary barrier to achieving glycaemic objectives in patients with type 1 diabetes and insulin-requiring type 2 diabetes is hypoglycemia. Risk factors for hypoglycemia in insulin-using patients include lower HbA1c 2, hypoglycemia unawareness, older age, longer duration of diabetes, renal insufficiency, and prior hypoglycemia.
2.*Weight gain* is one of the most common side effects of insulin therapy. Weight gain may result from frequent hypoglycemia episodes, in which patients overeat in reaction to hunger and take extra calories to compensate for the low blood sugar.
3.*Injection site reactions (ISRs)* are among the most common adverse effects of insulin therapy. Usually, concentration or pH causes local allergic responses and inflammation.
4.*Allergic reactions(redness, swelling, hives);*allergic reactions are a potential adverse reaction of insulin therapy.Systemic and local allergic reactions and Anaphylaxis are types of allergic reactions

- **Contraindications:**Hypersensitivity to insulin, Diabetic ketoacidosis
- **Insulin Storage:**Refrigerate at 2-8°C (36-46°F), Avoid freezing, Protect from light.

Rapid acting insulin products are:Lispro, Aspart, Glulisine
Insulin Liproso (Brand Name:Humalog)
Generic name:Insulin Lepro
Dosage form:injection 100 units/ml

Regular acting Insulin products are:Humulin, Iletin, Novolin, Relion, Velosulin.
Insulin humalin(brand name:Humalin R.)
Generic name:Insulin Regular
Dosage form:Injection 100 units/ml

Intermediate acting Insulin products are:Neutral protamine Hagedorn or NPH or Isophane.
Insulin NPH (Brand name:Humalin N,Novalin N)
Generic name:Insulin NPH
Dosage form:Injection,suspension 100 units/ml

Long-acting Insulin products are:Detemir, Degludec, Glargine.
Insulin Detemir(Brand name:Levemir)
Generic name:Insulin Detemir
Dosage form:Injection 100 units/ml.(9)

Category/Nameof Insulin	Brand Name (manufacturer)	Preparation(s)
Rapid-Acting		
Insulin Lispro	Humalog	Vial, cartridge, pen
	Admelog	Vial, pen
	Lyumjev	Vial, pen
Insulin Aspart	Novolog	Vial, cartridge, pen
	Fiasp	Vial, cartridge, pen
Insulin Glulisine	Apidra	Vial, pen
Technosphere insulin	Afreeza	Inhaler
Short-Acting		
Regular Human	Humulin R	Vial
	Novolin R	Vial
Intermediate-Acting		
NPH Human	Humulin N	Vial, pen
	Novolin N	Vial, pen
Long-Acting		
Insulin Detemir	Levemir	Vial, pen
Insulin Glargine	Lantus	Vial, cartridge, pen
	Basaglar	Pen
	Toujeo	Pen
Insulin Glargine-yfgn	Semglee	Vial, pen
Insulin Degludec	Tresiba	Pen
Insulin Mixtures		
NPH/Regular (70%/30%)	Humulin 70/30	Vial, pen
	Novolin 70/30	Vial, pen
Protamine/Lispro (50%/50%)	Humalog Mix 50/50	Vial, pen
Protamine/Lispro (75%/25%)	Humalog Mix 75/25	Vial, pen
Protamine/Aspart (70%/30%)	Novolog Mix 70/30	Vial, pen

Pharmacokinetic

Absorption

- Bioavailability:
  - NO ORAL BIOAVAILABILITY
  - SC, 1M: good.
  - Nasal: good (investigational).

Distribution :

- Bound in plasma:< 5%.
- Vd (70 Kg):. 15 L.

Biotransformation

- All insulin is *metabolized* in the liver, kidneys, and muscles (internalized with insulin receptors and destroyed intracellularly)
- (50% of insulin secreted by the pancreas into the portal vein does not reach the general circulation).

Excretion:

- Total Clearance: 800-2500 mL/min (70 Kg)

Type 2 DM: Oral antidiabetic drugs

a) Biguanides:
b)Sulfonylurea
c) Alpha-glucosidase inhibitors
d) Dipeptidyl peptidase-4 inhibitors (DPP-4I)
e) Thiazolidinediones (TZD)
f)Sodium–glucose cotransporter-2 inhibitors (SGLT-2I)

a)Biguanides: Metformin, Chlorproguanil, Chlorhexidine, Polyaminopropyl biguanide and Polyhexanide, Buformin and Phenoformin, Proguanil.(3)

Pharmacokinetics: Metformin is quickly absorbed from the small intestine. Metformin has a half-life of approximately 2 to 4 hrs.. Metformin is not bind to plasma proteins, but does partition into erythrocytes. Metformin is not metabolized and is excreted by the kidneys as the active compound.(14) changes pending.

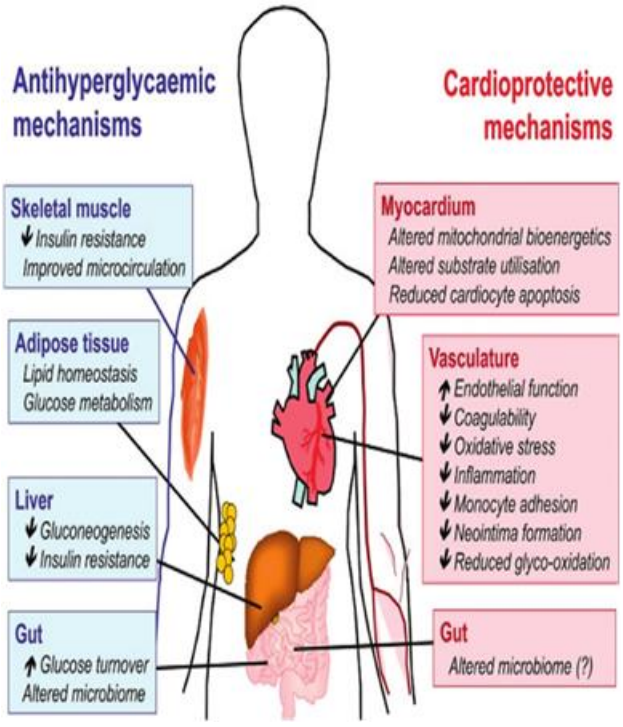


Fig no. 7: Antihyperglycaemic & Cardioprotective Mechanisms of action of Biguanides

Mechanism of action: Metformin caused the liver AMPK to become active, which decreased acetyl-CoA carboxylase (ACC),

increased fatty acid oxidation and suppressed theexpression of lipogenic enzyme.

Metformin-mediated AMPK activation

In skeletal muscle, metformin-mediated AMPKactivation promotes glucose transporter 4 translocation to the cell membrane,

Increasing glucose uptake. Ultimately, these effects reduce insulin resistance.
They also inhibit the expression of sterol regulatory element binding
protein-1c (SREBP-1), which inhibits the synthesis of fatty acids.(12)

Adverse reaction: Diarrhea, vomiting, dyspepsia, flatulence, metallic taste, weight loss.

Contraindications: Renal disease, heart failure requiring pharmacologic therapy, acute or chronic metabolic acidosis, active liver disease.(9)

b) Sulfonylurea: Sulfonylureas are used in conjunction with diet and exercise to treat patients with type 2 diabetes mellitus. Although sulfonylureas are sometimes used as monotherapy, they are more commonly used in combination with other oral anti-diabetic medications, sometimes in the same formulation, in patients who do not meet glycemic goals. General dosing recommendations include starting with a low dose and increasing it in accordance with patient response while monitoring for the signs of hypoglycemia, a frequent side effect. Be cautious when working with patients who have liver or kidney impairment. The range of HbA1c declines is 1% to 2%.(2)

Examples:1st generation: Chlorpropamide (long acting), Tolbutamide (short acting), Acetohexamide, Carbutamide, Glycinamide, Metahexamide, Tolazamide.
2nd generation: Glipizide, Glimepride, Glibenclamide, Gliburnuride, Glyclazide, Gliquidone, Glisopexide and Glyclopyramide.(3)

Mode of action: Sulphonylureasmaintain the body's blood glucose levels by directly promoting the release of insulin from pancreatic β-cells. Using a photoswitchable(photoactive) sulfonylurea, the sulfonylureas produce their hypoglycemic effects through a variety of mechanisms that can be broadly divided into three categories: pancreatic, extra-pancreatic, and optical control of insulin release.(14)

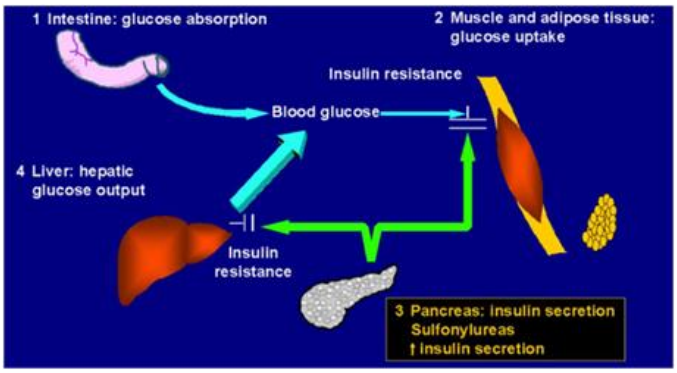


Fig.no. 8: Mechanisam of action of Sulfonylurea

Pancreatic mechanism:

The primary action of all sulfonylureas is to stimulate the release of insulin from β-cells.

↓

They act by affecting the ATP-sensitive potassium (KATP) channel [sulfonylurea receptor (SUR1) and potassium channel].

↓

On binding to SUR1, potassium efflux is blocked, leading to depolarization of the membrane.

↓

This depolarization opens voltage-dependent calcium channels, resulting in an influx of calcium.

↓

At higher intracellular calcium concentrations, calcium-sensitive proteins act to promote the release of stored insulin from the β-cells.(14)

Side Effects: Hypoglycemia (most common), Weight gain, Increased risk of cardiovascular events, Allergic reactions (rash, itching), Liver damage (rare)

Contraindications: Type 1 diabetes, Diabetic ketoacidosis, Severe kidney or liver disease, Pregnancy (unless benefits outweigh risks), Hypersensitivity to sulfonylureas

Interactions: Warfarin and other anticoagulants,Beta-blockers and other cardiovascular medications, Thiazide diuretics, Corticosteroids, Estrogens and progestins

Pharmacokinetics:

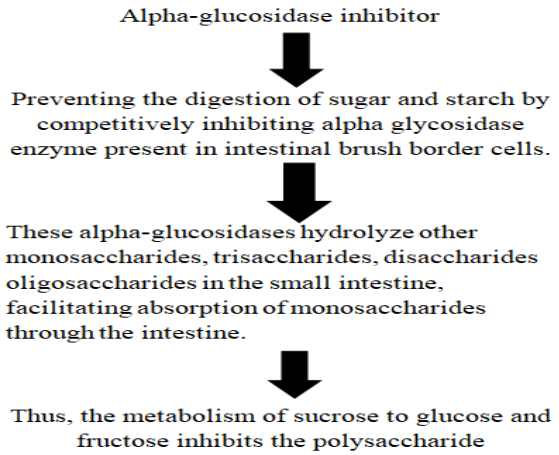
All sulfonylureas are effectively absorbed from the gastrointestinal tract, although food and hyperglycemia can reduce the absorption. Given the time required for absorption, sulfonylureas with short half-lives may be more effective when given 30 minutes before eating. Sulfonylureas in plasma are largely bound to protein, especially serum albumin. The second-generation agents are approximately a hundred times more potent than those in the first generation. Because their half-lives are 3–5 hrs, their hypoglycemic effects persist for 12–24 hrs, and they often can be administered once daily. All sulfonylureas are metabolized by the liver, and the metabolites are excreted in the urine.(14)

c) Alpha glycosidase inhibitor:eg, Acarbose, Miglitol, Voglibose,

Acarbose, Voglibose, and Miglitol are probably safe and effective. Although they have not been used extensively to treat type 2 DM. These medications work best for postprandial hyperglycemia, and they shouldn't be used in patients who have severe renal impairment.(16)

In the upper intestine, alpha-glucosidase enzymatically breaks down polysaccharides and disaccharides into monosaccharides. By reversibly blocking the enzymatic conversion of complex carbohydrates to simple, absorbable sugars, alpha-glucosidase inhibitors lower postprandial hyperglycemia without increasing the risk of hypoglycemia, which in turn lowers HbA1c.(15)

***Mechanism of action*:**



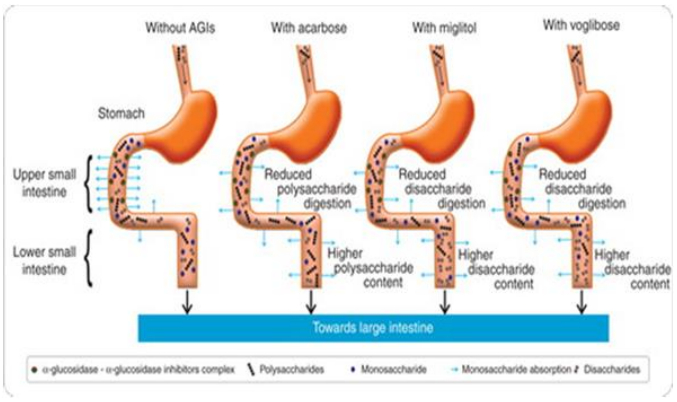


Fig.no. 9: Therpeutic potential of Alpha glycosidase inhibitor in Type 2 diabetes

Sideeffects:gastrointestinal complains (flatulence, abdominal discomfort, diarrhea),Hypoglycemia(rare), Vomiting is a common side effects of therapy with α-glucosidaseinhibitors.(14)

Contraindications: Inflammatory bowel disease(IBDs), conditions associated with malabsorption, Severe renal failure.

Pharmacokinetics: α-glucosidase inhibitors are a mild antihyperglycemic and not a hypoglycemic. It may be used as an adjuvant to diet (with or without a sulfonylurea) in obese diabetics. It is minimally absorbed, but produces loose stool in about 50% patients due to fermentation of unabsorbed carbohydrates. These drugs are excreted by the kidneys.(14)

d) dipeptidyl peptidase-4 inhibitors (DPP-4I):

The *drugs are Linagliptin, Saxagliptin and Sitagliptin.*

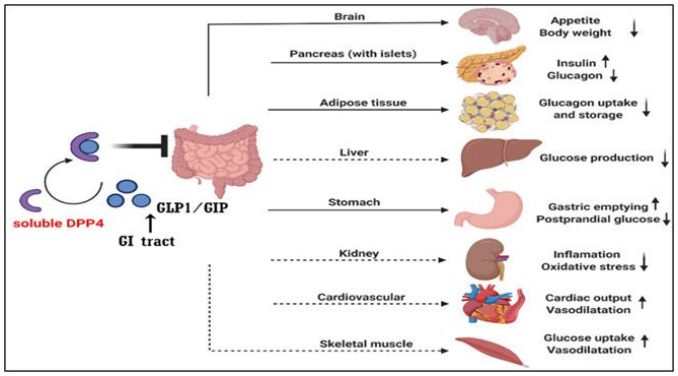


Fig no. 10: DPP4 affecton different organs

Mechanism of Action :Mechanism of action for drug class,

Inhibition of dipeptidyl peptidase-4(DPP-4) enzyme. it inhibits the breakdown of active GLP-1 through the inhibition of the enzyme DPP-4.

↓

Active GLP-1 is release from α cells of pancreas in response to food intack.it regulates blood glucose by increasing secretion of insulin from pancreas.

↓

Increase insulin secreation, decreased glucagon secreation, delayed gastric empyying.(9)

Side effects:Nasopharyngitis (inflammation of nasal passage and pharynx), headache, cough, fatigue, diarrhea, Abdominal pain, Constipation, Increased risk of hypoglycemia.
Contraindications: Hypersensitivity, Type 1 diabetes, Sever renal impairment.

Pharmacokinetics:

DPP-4 inhibitors are typically absorbed from the gastrointestinal tract. They have varying rates of bioavailability.Most of these drugs are absorbed rapidly, but food may influence the rate of absorption. DPP-4 inhibitors are generally largely distributed all through the body, including tissues and plasma.The volume of distribution (Vd) varies, with linagliptinhaving a higher distribution to tissues (Vd ~ 320 L), while others like sitagliptin have lower volumes of distribution (Vd ~ 200 L).DPP-4 inhibitors undergo varying degrees of metabolism in the liver**.**Sitagliptin undergoes minimal metabolism, with the greater part of the drug excreted unchanged via the kidneys**.**Vildagliptin, on the other hand, is metabolized by cytochrome P450 enzymes (CYP3A4/5) and also has some metabolic pathways that are influenced by renal function.Elimination of DPP-4 inhibitors is mostly renal. Drugs like sitagliptin, alogliptin, and vildagliptin are predominantly eliminated by the kidneys, making renal function an important consideration for dosing adjustments.(28,29)

e) Thiazolidinediones (TZD):

Thiazolidinedione work by improving insulin sensitivity, making the body's cells more responsive to insulin. This helps reduce blood sugar levels.The two main thiazolidinediones used in diabetes management are **pioglitazone** and **rosiglitazone**. These drugs activate peroxisome proliferator-activated receptor gamma (PPAR-γ), which plays a key role in regulating glucose and lipid metabolism.

- ***Mechanism of Action:***

Peroxisome proliferator-activated receptor gamma (PPAR-γ):
TZDs act as predominantly through PPAR-γ activation.

↓

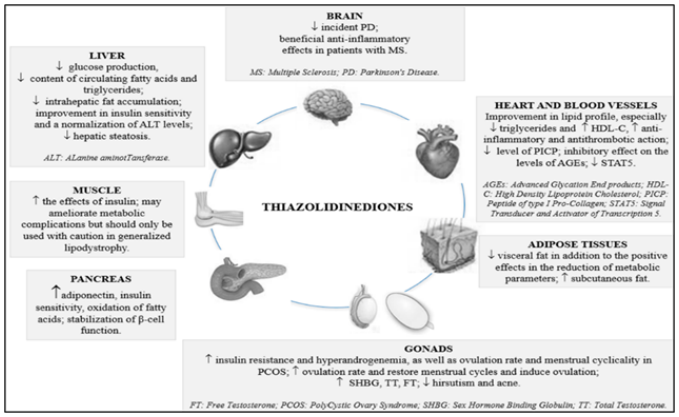
This receptor regulates genes associated in glucose and lipid metabolism, increasing insulin sensitivity in peripheral tissue

Upon activation of PPAR

↓

TZDs increase the expression of genesthat enhance insulin sensitivity, promoting better glucose uptakeby muscle and adipose tissue, and reducing glucose production in the liver.

Side effects: weight gain(This is a common side effect due to fluid retention and increased fat storage, risk of bone fracture(osteoporosis), cardiac failure particularly in patients with pre-existing heart conditions.



Contraindications: Heart failure, Active bladder cancer(for pioglitazone), Sever hepatic impairment, Pregnancy, History of osteoporosis or fracture.(25,26)

Pharmacokinetics: Pioglitazone is well absorbed and reaches peak plasma concentration in about 2 hours. Plasma protein binding is greater than 99% at a single dose distribution volume of 0.63 l/kg. Pioglitazone is metabolized to active metabolites by CYP3A4 and CYP2C8. All pioglitazone-related metabolites have a half-life of 16 to 24 hours, whereas

pioglitazone has a serum half-life of 3 to 7 hours. Urine contains 15–30% of the oral dose, mostly in the form of metabolites and their conjugates.The remainder is probably excreted in the bile. Rosiglitazone is also well absorbed with an absolute bioavailability of 99%. Peak plasma concentrations occur approximately 1 hour after oral administration. Rosiglitazone is highly bound to plasma proteins (99.8%) and has a steady-state volume of distribution of approximately 17.6 L. Rosiglitazone is metabolized primarily in the liver by CYP2C8 and, to a lesser extent, by CYP2C9 to the least active metabolite. Rosiglitazone has a half-life of 3 to 4 hours and is excreted primarily through urine (64%) and to a small extent through feces (23%).(4)

f) sodium–glucose cotransporter-2 inhibitors (SGLT-2I):

SGLT2 inhibitors help lower HbA1c (a measure of long-term blood sugar control), reduce body weight, and lower systolic blood pressure. These properties make them a useful supplement to other diabetes treatments, especially for people with type 2 diabetes. Weight loss is a beneficial effect, as most other antidiabetic drugs cause weight gain, making diabetes more difficult to manage(3)

e.g: Canagliflozin ,Dapagliflozin, Empagliflozin, Ertugliflozin.(21)

Mechanism of action:

Reversibile inhibition of the sodium dependent glucose co transporter (SGLT-2) in proximal tubule of the kidney

↓ Reduced glucose Reabsorption in kidney.

The drugs specifically inhibit the SGLT2 protein, which is responsible for about 90% of glucose reabsorption in the kidney.

↓

When this protein is blocked, glucose is excreted via urine, leading to a reduction in blood glucose levels.(23)

Side effects:

- *Genital infections*: Because these drugs increase glucose in the urine, they can promote bacterial and fungal infections in the genital area.
- *Urinary tract infections (UTIs):* Increased glucose in urine may also promote the growth of bacteria that can lead to UTIs.
- *Dehydration:* SGLT2 inhibitors have a mild diuretic effect, leading to increased urination and potential dehydration.
- *Diabetic Ketoacidosis (DKA):* Although rare, there have been reports of DKA in patients using SGLT2 inhibitors, even in those with normal blood glucose levels.
- *Bone Fractures*: There is some evidence suggesting that long-term use of canagliflozin, in particular, may increase the risk of bone fractures (22)

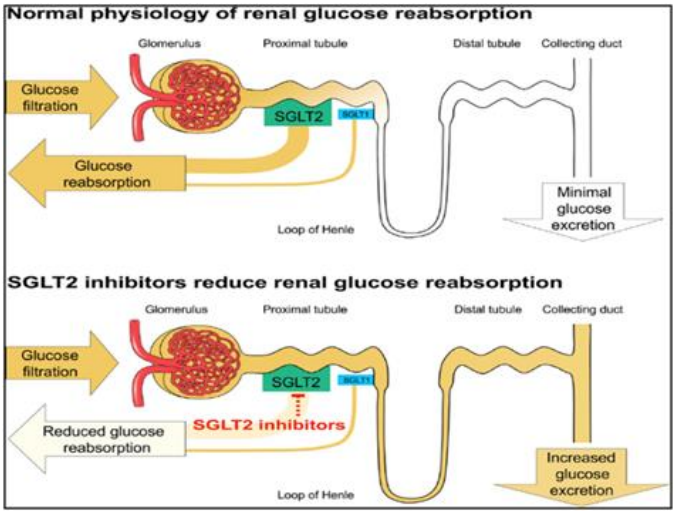


Fig. no. 12: SGLT-2I affects renal glucose reabsorption or nephron

Contraindications:Sever renal impairment, Hypersensitivity, Diabetic ketoacidosis, Pancreatitis, Urinary tract infections, Hypotension.

Pharmacokinetics:

SGLT2 inhibitors are generally well absorbed after oral administration. Peak plasma concentrations (C_max) typically occur within 1 to 2 hours after dosing for most drugs in this class.The bioavailability of these drugs can vary, typically ranging from 60-80%, depending on the specific agent.After absorption, these drugs are widely distributed in the body, with volumes of distribution (Vd) ranging from 50 to 100 L for many agents in the class.They have a moderate to high protein binding (approximately 90% for many SGLT2 inhibitors), meaning that they bind to plasma proteins such as albumin during circulation.Most SGLT2 inhibitors undergo extensive metabolism in the liver, primarily via glucuronidation or cytochrome P450 enzymes, although the

extent of metabolism can vary between different agents.Some drugs in this class, like canagliflozin, are metabolized via CYP450 3A4, whereas others, like empagliflozin, undergo limited metabolism.SGLT2 inhibitors are primarily eliminated via the kidneys. The drugs are excreted in both the urine (as unchanged drug or metabolites) and feces.(24)

DIABETES MELLITUS DIETARY MANAGEMENT

The Dietary Principle that there should be a sufficient amount of vitamins (mostly C and E) in the diet, along with foods that are low in calories, low in sugar, high in protein, high in fiber, and moderately high in fat. In this situation, minerals like zinc ought to be recommended (Tewari, 2019).
Sufficient calorie content Both diabetic and non-diabetic patients should follow proper dietary guidelines, which include:

• Limiting carbohydrate intake in all situations and balancing protein, carbohydrate, and fat intake.
• It should be as close to normal as is practical.
• At regular intervals, food should be portioned into portions of a similar size.
• Cut back on fat and carbs to cut down on overall caloric intake.
• The patient should be counseled to continue eating the same foods every day.

Diagnosis:

Tests like the oral glucose tolerance test and the HbA1c test are necessary to diagnose patients with diabetes or prediabetes. Obesity, high blood pressure, and a family history of diabetes are high risk factors for diabetes [13]. FPG values were the primary emphasis of the American Diabetes Association's(ADA) 1997 guidelines for diagnosing factor D M. WHO prioritises OGTT [14]. The following kinds of testing are used to diagnose diabetes:

1. Fasting plasma glucose: Prior to the test, you must fast for eight hours. 126 mg/dL or above is considered diabetic.
2. Two hours following a 75 g oral glucose load, such as an OGTT, plasma glucose level should be 200 mg/dL or greater.
3. Random plasma glucose and hyperglycemia symptoms: 200 mg/dL or more.
4. HbA1c, or glycated haemoglobin, 24 mmol/mol or higher. (27)

Prevention:

- Type 1 diabetes could not preventive because it is due to auto immune disease, it should control by some medication use(oral hypoglycemic agents).
- Type 2 diabetes should be preventable or delayed by maintaining the normal body weight, physical activity, eating a healthy diet
- Limiting surgary beverages and eating less red meat and other source of saturated fat can also help the prevent diabetes.
- Medication used to treat diabetes do so by lowering blood glucose level. There are different classes of oral hypoglycemic agent that are used to treatment of diabetes mellitus. Metformin is the first choice in people with diabetes, generally output and insulin resistance.(27)

Conclusion :

More than four hundred million of people around the world had to face a challenging health condition that is diabetes. At the same time, a large number of this population live in India - seventy-four million. In India, this percentage of people means that at least 9.3% of the population from age 18 to 69 of both sexes has diabetes type 2. Due to the two main types of diabetes; known as Type 1 and Type 2, they come from different sources whereby, Type 1 arises from the autoimmune destruction of beta cells found in the pancreas and, Type 2 in most cases is associated with elevated levels of insulin often linked to obesity as well as lifestyle behaviours. Despite there being several options that have been and are already used in the treatment of diabetes including the use of insulin in Type 1 and the use of oral drugs for management of Type 2, to control glucose abnormality for both types, let alone all other objectives, may not be achievable and may come along with a number of disadvantages. It is concerned that the number of people with diabetes is increasing for various reasons and that more emphasis should be placed on raising public awareness, prevention, and management in its various aspects and its complications so much as that of the heart failure and renal failure. The epidemic of diabetes in society has led to there being such changes and consequently there exists a critical need for diabetes-related methods that incorporate a more holistic view and bear the potential to elicit positive social results while nonetheless improving on the health literacy of individuals living with this medical condition.

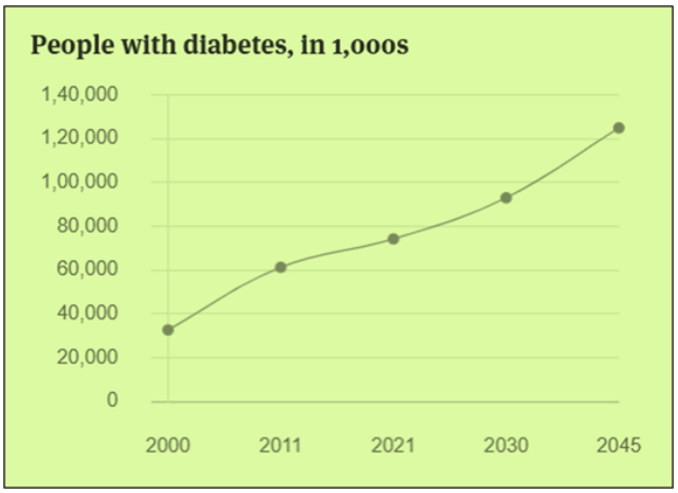


Table no.2 : Estimates report of Diabetes in India 2000 – 2045 provide by International Diabetes Federation(29)

At a glance	2000	2011	2021	2030	2045
Diabetes estimates (20-79 y)					
People with diabetes, in 1,000s	32,674.4	61,258.4	74,194.7	92,973.7	124,874.7
Age-adjusted comparative prevalence of diabetes, %	-	9.0	9.6	10.4	10.8
People with undiagnosed diabetes, in 1,000s	-	-	39,397.4	-	-
Proportion of people with undiagnosed diabetes, %	-	-	53.1	-	-
Impaired glucose tolerance (IGT) estimates (20-79 y)					
People with IGT, in 1,000s	-	20,467.5	40,143.8	50,045.4	65,557.3
Age-adjusted comparative prevalence of IGT, %	-	3.0	5.4	5.6	5.8
Impaired fasting glucose (IFG) estimates (20-79 y)					
People with IFG, in 1,000s	-	-	75,123.9	85,065.3	95,598.7
Age-adjusted comparative prevalence of IFG, %	-	-	7.8	8.2	8.3
Mortality attributable to diabetes (20-79 y)					
Deaths attributable to diabetes	-	983,203.0	647,831.0	-	-
Proportion of diabetes-related deaths in people under 60 y, %	-	-	2.8	-	-
Type 1 diabetes estimates in children and adolescents					
New cases of type 1 diabetes (0-14 y), in 1,000s	18.1	-	19.2	-	-
New cases of type 1 diabetes (0-19 y), in 1,000s	-	-	24.0	-	-
Type 1 diabetes (0-14 y), in 1,000s	66.9	-	124.6	-	-
Type 1 diabetes (0-19 y), in 1,000s	-	-	229.4	-	-
Hyperglycaemia in pregnancy (HIP) (20-49 y)					
Live births affected by HIP	-	-	6,182,373.9	-	-
Prevalence of gestational diabetes mellitus (GDM), %	-	-	29.3	-	-
Live births affected by other types of diabetes first detected in pregnancy	-	-	220,541.9	-	-
Live births affected by other types of diabetes detected prior to pregnancy	-	-	194,791.2	-	-
Diabetes-related health expenditure					
Total diabetes-related health expenditure, USD million	-	-	8,485.8	10,305.5	12,834.3
Total diabetes-related health expenditure, ID million	-	-	32,054.9	38,928.6	48,481.1
Diabetes-related health expenditure per person, USD	-	68.0	114.4	138.9	173.0
Diabetes-related health expenditure per person, ID	-	-	432.0	524.7	653.4
Demographics					
Total adult population (20-79 y), in 1,000s	567,714.0	737,003.3	893,910.0	1,022,119.2	1,154,012.2
Population of children (0-14 y), in 1,000s	361,182.0	-	359,208.6	-	-
Population of children and adolescents (0-19 y), in 1,000s	-	-	485,464.9	-	-
Complications of diabetes					
Microvascular	• Nephropathy: 5.9% & • Retinopathy: 0.8% • Neuropathy: 10.6%				
Macrovascular	• Coronary artery disease: 2.5% • Cerebrovascular disease: 0.3% • Peripheral artery disease: 0.0% • Heart failure: 0.2%				

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